REMARKS

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 1-18 and 22-24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The grounds are discussed below.

Rejection i. "It is not clear which active ingredient is 'the active ingredient'. There is no antecedant basis for 'the active ingredient'."

Claims 1 and 18 have been amended to change "the active ingredient" to "said at least one of the first and second active ingredients." It is believed that this amendment overcomes the rejection.

Rejection ii. "Applicant argues that the powder embodiment makes sense but if one of the 'active ingredients' is coated, how can it then be a powder? When the active ingredient is in a coating suspension then it is not in a powder and when the active ingredient is granulated the coating is gone or at least damaged, thus the 'protective barrier' is no more."

Applicant believes that the word "powder" accurately describes a granular formulation in which one of the ingredients is a finely divided powder and another consists of granules having a coating. Remington's Pharmaceutical Sciences (1970), Chapter 86, "Powders" (Alvin Felmeister, PhD), begins:

> "Although there is no official definition of powders, this term generally refers to those pharmaceutical dosage forms that are made up of more or less finely divided, dry, solid material. The particle size of such powders may vary from the very fine, as in aerosols and insufflations, to the coarse, as in effervescent granules and some crude drug

preparations. However, it should be noted that, in addition to constituting a class of pharmaceutical preparations, powders also serve as the starting point for other important dosage forms including tablets, capsules, and suspensions." (p. 1626)

The examples are clear that in the exemplary processes of making the powders, the granules are coated, rather than the coated material being granulated as seems to be suggested by the Examiner. Thus, the granules including their protective coating are a part of the powder. The production of a powder in which one of the active ingredients is coated is described in Example IV at page 21 of the specification.

Rejection iii. "Applicant argues that there is no protective barrier as there is a physical space. While this is interesting, something is still holding the 'active ingredients' in place."

It is believed that this rejection relates to claim 15. Claim 15 has been amended to require that both the first region and the second region include an excipient which will function to hold the region together.

Rejection iv. "Also it is confusing which 'active ingredient' is 'the active ingredient', i.e. no antecedant basis for 'the active ingredient'. Further, there is no antecedant basis for applicant's new amendment of 'in said at least one layer'. It is not clear which layer applicant is referring to."

It is believed that these rejections relate to claim 16. That claim has been amended to remove the questioned language and simplify the language of the claim.

CLAIM REJECTIONS - 35 U.S.C. § 102

Claims 1, 3, 6-8, 15-18 and 22-24 have been rejected under 35 U.S.C. § 102(b) as being anticipated by FR 6855. This rejection is respectfully traversed.

The claims are directed to a formulation which includes an anti-infective agent and a microorganism which is "**susceptible to said anti-infective agent.**" FR 6855 explicitly utilizes lactic ferments "**rendered antibiotic resistant.**" (last paragraph of first page of translation). This reference therefore neither teaches nor suggests the present invention.

In their previous response, applicants pointed out that tetracycline is well-known to be a bacteriostatic drug, rather than a bactericidal. The Examiner has questioned applicants' statement and has objected that applicants have provided no evidence to support their statement. It is believed that the statement is of such a well-known fact that no evidence was necessary. The requested evidence is enclosed. Attached are excerpts from four standard references. Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8th Edition, p. 1117: "*In vitro*, these drugs [tetracyclines] are primarily bacteriostatic. Only multiplying microorganisms are affected." O'Grady, et al., "Antibiotic and Chemotherapy: Anti-infective agents and their use in therapy," Chapter 48 (Tetracyclines) p. 469: "Their [tetracyclines'] activity is essentially bacteriostatic." Martindale, "The Complete Drug Reference," p. 260, col. 1: "Antimicrobial Action: The group of tetracycline antibiotics is mainly bacteriostatic, ..." Satoskar, et al., "Pharmacology and Pharmacotherapeutics," p. 612: "Antibacterial activity: Tetracyclines and their semi-

synthetic derivatives have similar antibacterial activity. These drugs are essentially bacteriostatic ...."

The Examiner further states that "it is clear from FR 4430 (of record) that tetracycline maintains both bacteriostatic and bactericidal action against pathogenic germs such as *Lactobacillus acidophilus*." This is clearly inaccurate. Lactobacillus acidophilus is not a pathogen, it a useful organism (a probiotic). FR 4430 utilizes "lactic bacilli rendered resistant to the antibiotic with which they are combined. At the same time, the antibiotic maintains its bacteriostatic & bactericidal action against pathogenic germs which cause infections illnesses, for the treatment of which the antibiotic is selected." This is certainly not a statement that tetracycline is bacteriocidal against lactic bacilli.

The examiner also states that "tetracycline is a known antibacterial/antibiotic, thus it meets the requirements of the claims." This is not so. The claim calls for an organism which is **susceptible to said anti-infective agent**. The organism disclosed by FR 4430 is not susceptible to the tetracycline used in this reference. Neither the problem addressed by the present invention nor its solution is shown or suggested by this reference.

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To shorten the prosecution of this application, and without prejudice to their right to file divisional applications directed to the original subject matter of claim 1, applicants have further modified "formulation" claim 1 to insert the limitation that the anti-infective is "**selected from the group consisting of betalactams, fluoroquinolones, macrolides, and betalactamase inhibitors**." Likewise, "tablet" claim 15 has been amended to set out that the "**the first and s cond active**

ingredi nts ar physically s parated in the tablet by a coating." Nothing in FR 6855 or any of the other art of record discloses or suggests the combination as now claimed.

Claim 1 has also been rejected under 35 U.S.C. § 102(b) as being anticipated by FR 5247. This rejection is respectfully traversed.

Published application FR 5247 also relates to a combined formulation in which the antibiotic is tetracycline and the micro-organism is not susceptible to the antibiotic. Again, the claim as now written clearly distinguishes over this disclosure. Moreover, tetracycline is a bacteriostatic drug, rather than a bactericidal, and because the bacteria in the formulation are not actively growing, there is no reason to believe that tetracycline would have any effect on the organisms in the formulation. FR 5247 also suggests using resistant organisms and suggests that their resistance may disappear. (The latter suggestion is unlikely, although this is not particularly relevant to the issue of anticipation.) It therefore does not either disclose or suggest the formulation of the present invention, which avoids the use of resistant organisms. Because of the formulation described in FR 5247, neither the problem addressed by the present invention nor its solution is shown or suggested by this reference. As noted above, the claims are directed to a stable formulation which includes an anti-infective agent and a microorganism which is "susceptible to said anti-infective agent."

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1-18 and 22-24 have been rejected under 35 U.S.C. § 103(a) as being obvious over FR 5247 in view of FR 6855 and further in view of Black et al. The

same claims have been rejected as obvious over FR 6855 in view of Black et al. These rejections are respectfully traversed.

The primary references teach as above and do not suggest the invention as claimed for the reasons set out above. Black et al. teaches nothing that would make the present invention obvious.

Contrary to the Examiner's position, Black et al. teaches administering ampicillin and microorganisms in **separate** formulations at **separate** times. The Abstract of the Black et al. paper says simply that "10 volunteers received 500 mg ampicillin tablets t.i.d. together with capsules containing lactic acid producing bacteria ... for 7 days." Later in the paper, p. 248, however, it is made clear that the tablets and capsules were intended to be taken at different times: "During the administration of ampicillin, 10 volunteers were given a capsule containing 4 x 10^9 live lyophilized microorganisms of 2 different bacterial species ... 2 h after the ampicillin administration t.i.d. for 7 days." If this reference teaches anything, therefore, it is that ampicillin and bacteria should not be ingested at the same time. It suggests nothing about making a stable single dose oral formulation.

Black was used to show that one can use ampicillin for similar use.

Applicants' specification, however, sets out that the state of the art has included giving organisms along with an anti-infective. That approach, however, leads to non-compliance by the patient.

> The organisms named above can be used to treat diarrhea when it occurs. They can also be used to prevent diarrhea.[14, 16, 18] Commercially available preparations include lactobacillus alone (Lactiflora, Lactobacil. Lactocap, Lactovit, Sporlac) or in combination with streptococcus (Lacticyn) or Sacchromyces (Laviest). To prevent diarrhea, organisms are given along with the anti-infective agents. This requires consumption of a minimum of two

different drugs, i.e. an anti-infective agent and an organism. This decreases compliance of a patient.

Reference Nos. 14,16,18 are reproduced below:

14. Biotherapeutic agents. A neglected modality for the treatment and prevention of
selected intestinal and vaginal infections. JAMA 1996 Mar 20; 275 (11) : 870-6
15. The pharmacologic principles of medical practice, Krantz & Carr
16. Prevention of beta-lactam-associated diarrhea by saccharomyces boulardii
compared with placibo. Am. J. Gastroenterol. 1995 Mar ; 90 (3): 439-48
18. Prophylaxis against ampicillin-associated diarrhea with a lactobacillus preparation. Am. J. Hosp. Pharm. 1979 Jun ; 36: 754-757

The purpose of the present invention, however, is to provide a **stable, single dose** oral formulation that does not require the patient to ingest two different medications. In particular, as set out at page 2, lines 14-17: "The present invention is directed to a formulation wherein anti-infective agents and susceptible viable organisms are combined in such a way that microorganisms, though susceptible to anti-infective agent, remain viable for the shelf life of a formulation and/or until they are consumed."

None of the references suggests combining an anti-infective with a **susceptible** micro-organism in a **single** formulation. Thus, nothing in the references, alone or combined, suggests the invention as set out in the claims.

The dependent claims set out further non-obvious features of the invention. By way of example, the combinations of claim 2 and 22 set out combinations with anti-infectives (antibiotics) that are certainly not suggested by the prior art. The organisms, ratios, the coating of granules, the coating materials, and the physical

configurations of the formulations set out in the dependent claims are also not suggested by any of the cited art, alone or in combination.

The present amendment, if entered, overcomes the rejections under 35 U.S.C. § 112. It is therefore respectfully requested that the amendment be entered and the case passed to issue.

Should the Examiner not be prepared to allow all of the claims, he is again requested to call applicants' undersigned attorney to arrange an interview.

Respectfully submitted,

J. Philip Polster
Registration No. 24,739
POLSTER, LIEDER, WOODRUFF
& LUCCHESI, L.C.
763 South New Ballas Road
St. Louis, MO 63141
(314) 872-8118
(314) 991-2178 (fax)